UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,497	11/13/2001	Simeon M. Wrenn Jr.	12636-876	8627

21971 7590 04/08/2003

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 943041050

EXAMINER	
YOUNG, JOSEPHINE	
ART UNIT	**PAPER NUMBER**
1623	8

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/763,497	WRENN JR., SIMEON M.	
	Examiner	Art Unit	
	Josephine Young	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,26,27,29 and 38-58* is/are pending in the application.

4a) Of the above claim(s) *1-10 and 38-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-24,26,27,29 and 44-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *8,10* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-10 and 38-43, drawn to compositions comprising an acid-labile 2'-deoxyadenosine analog and an agent that inhibits the 2'-deoxyadenosine analog from decomposing by reducing the acid concentration in the stomach, classified in class 514, subclasses 45, 46, 47, 48.

II. Claims 11-24, 26-27, 29 and 44-58, drawn to methods of treating a patient by administering, together or separately, a 2'-deoxyadenosine analog and an agent that inhibits the 2'-deoxyadenosine analog from decomposing by reducing the acid concentration in the stomach or using said compositions, classified in class 514, subclasses 45, 46, 47, 48.

The inventions are distinct, each from the other because of the following reasons:

Groups I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the process for treating a patient orally using a 2'-deoxyadenosine analog and an agent that inhibits the 2'-deoxyadenosine analog from decomposing by reducing the acid concentration in the stomach can be practiced with a

materially different compound or composition, for example a known orally available antiviral such as epivir or combivir in tablet form.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their recognized divergent subject matter, restriction for examination purposes as indicated is proper. A reference for one group could not reasonably be expected to be a reference for the other. Further, searching both of the inventions constitutes a burdensome search, as a thorough search comprises a search of foreign patents and non-patent literature, as well as the appropriate U.S. patent classifications. To search the two independent and distinct inventions, set forth supra, would indeed impose an undue burden upon the examiner in charge of this application.

During a telephone conversation with Applicant's representative, Shirley Chen, on March 21, 2003, a provisional election was made without traverse to prosecute the invention of Group II, claims 11-24, 26-27, 29 and 44-58. Affirmation of this election must be made by applicant in replying to this Office action.

Claims 1-10 and 38-43 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claim 13 recites an erodible matrix. However, the specification does not teach an erodible matrix per se. Instead, the specification is directed to elastomeric matrices (e.g. non-erodible, erodible, environmental agent ingression and degradable). See page 12, lines 23-26. While the term erodible matrix is well understood in the art, the specification fails to particularly disclose this dosage form.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below in In re Wands USPQ2d 14000. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention.

These factors include

(1) quantity of experimentation necessary,

(2) the amount of guidance presented,

(3) the presence or absence of working examples,

(4) the nature of the invention,

(5) the state of the prior art,

(6) the predictability of the art and

(7) the breath of the claims.

Claims 11-24, 26-27, 29 and 44-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of certain disease using a particular 2'-deoxynucleoside analog, does not reasonably provide enablement for treating all types of diseases using any 2'-deoxynucleoside analog. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With regard to factors (1) and (2) cited above, undue experimentation is required to determine which diseases unknown in the art at the time the present invention was made to be treatable by a particular 2'-deoxyadenosine analog would be effected by such 2'-deoxyadenosine analog. Further, undue experimentation is required to determine which particular 2'-deoxyadenosine analog would be useful in the treatment of that disease. There has not been provided adequate guidance in the written description for accomplishing and determining such.

With regard to factors (4), (5) and (6), it is noted that there is a great deal of unpredictability in the art. For example, while certain agents and compositions are known to treat certain disease, no effective agent or composition has been found for the treatment of all diseases. Therefore, the art at the time the invention was made fails to establish predictability with regard to the properties of the compositions needed to perform the scope of the methods as instantly claimed.

With regard to factors (3) and (7), it is noted that there are no working examples of any assay or treatment of a patient using the compositions of the present invention. There is not sufficient disclosure to support the breath of the claims. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves. See In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Further, claims 48 and 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the reduction of acid concentration in the stomach using an antacid, such as calcium carbonate, or a histamine H2 inhibitor, such as cimetidine, does not reasonably provide enablement for the reduction of acid concentration in the stomach using a proton pump inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With regard to factors (1) and (2) cited above, undue experimentation is required to determine which proton pump inhibitor would be useful for the reduction of acid concentration

in the stomach to protect an acid-labile 2'-deoxyadenosine analog for which the instant invention is applicable. There has not been provided adequate guidance in the written description for accomplishing such, as no proton pump inhibitor was assessed or even explicitly pointed out in the specification.

With regard to factors (4), (5) and (6), it is noted that there is a great deal of unpredictability in the art. For example, numerous compounds can be considered proton pump inhibitors, however, not all compounds would be viable in combination or alternation with a 2'-deoxyadenosine analog. Further, it is unclear which proton pump inhibitor with reduce the acidic environment of the stomach to the requisite degree. The art at the time the invention was made fails to establish predictability with regard to the properties of the proton pump inhibitor needed to perform the methods as instantly claimed.

With regard to factors (3) and (7), it is noted that there are no working examples of compositions comprising a proton pump inhibitor. There is not sufficient disclosure to support the breath of the claims. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves. See In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-24, 26-27, 29 and 44-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "2'-deoxyadenosine analog" in claims 11, 13-24, 26-27, 29, 44-52 and 54-58 renders the claims in which it appears indefinite. In the absence of the specific modification to the 2'-deoxyadenosine or distinct language to describe the analog or the chemical names of the 2'-deoxyadenosine analog of this invention, the identity of said 2'-deoxyadenosine analog would be difficult to describe and the metes and bounds of said method of treating a patient using a 2'-deoxyadenosine analog that Applicant regards as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims.

The phrase "treating a patient" in claims 11-20, 24, 26-27, 29 and 44-58 renders the claims in which it appears indefinite. In the absence of a particular disease to be treated, the identity of said patient would be difficult to describe and the metes and bounds of said treatment that Applicant regards as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims.

The term "proton pump inhibitor" in claims 48 and 58 renders the claims in which it appears indefinite. In the absence of the specific proton pump inhibitor or distinct language and/or chemical formula to describe class of compounds that would be considered a proton pump inhibitor of this invention, the identity of said proton pump inhibitor would be difficult to describe and the metes and bounds of said method of treating a patient using a proton pump inhibitor that Applicant regards as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11, 16, 20, 46-47, 50-52 and 56-57 are rejected under 35 U.S.C. 102(b) as being anticipated by patent EP 0 524 579 A1 to BRISTOL-MYERS SQUIBB COMPANY (BMS).

BMS teaches that the acid lability of 2,'3'-didoxypurine nucleosides, and in particular, 2',3'-dideoxyadenosine (ddA), 2',3'-dideoxyinosine (ddI) and 2',3'-dideoxyguanosine (ddG) and their triphosphates are well-known in the art. See page 2, lines 9-25. Approaches to improve the acid stability of these acid-labile antiviral nucleoside derivatives have involved enteric-coated formulations, inclusion of a buffer in the dosage form, and neutralization of the gastrointestinal tract just before drug ingestion by pretreatment with commercial antacids. Further, BMS teaches on page 3, lines 30-36, that the buffers applied as antacid agents include mixtures of water-insoluble antacid magnesium compounds with dihydroxyaluminum alkali metal carbonates or calcium carbonate, preferably with calcium carbonate. BMS discloses in Example 4, various oral tablet formulations with didanosine and calcium carbonate using microcrystalline cellulose and polyplasdone XL10 for use as antiviral agents.

Claims 11, 14, 16-17, 20, 24, 46, 49-50, 52 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by patents US 5,118,672 ('672) and US 5,159,067 ('067) both to SCHINAZI et al.

SCHINAZI teaches in column 30, line 66 to column 31, line 8 of the '672 patent and column 13, lines 52-63 of the '067 patent, that some compounds useful in methods to treat viral infection, such as 2',3'-dideoxyadenosine and 2',3'-dideoxy-N^6-methyladenosine, and their diphosphohexose derivatives are acid labile. Further, in the same passages, SCHINAZI teaches that if oral administration of these antiviral nucleoside analogs is desired, the compound must be provided in a composition that protects it from the acidic environment of the stomach, in combination with an antacid formulation and/or in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. In column 31, lines 19-39 and column 31, line 62 to column 32, line 9 of the '672 patent and column 14, lines 4-24 and column 14, line 47 to column 15, line 9 of the '067 patent, SCHINAZI discloses various pharmaceutical formulations, including various binders, coatings and controlled release formulations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 11-24, 26-27, 29, 46-47, 49-53 and 56-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over patent EP 0 524 579 A1 to BRISTOL-MYERS SQUIBB COMPANY (BMS) in view of patents US 5,310,732 to CARSON et al. and US 5,366,960 to GALLAGHER.

Applicant claims methods to treat a patient using acid labile 2'deoxyadenosine analogs, and in particular pentostatin or cladribine, and an agent that reduces that acidic environment of the stomach, and in particular an antacid such as calcium carbonate. In particular, Applicant claims methods to treat hematological malignancies, solid tumors sensitive to 2'-deoxyadenosine analogs or adenosine deaminase inhibitors and autoimmune diseases mediated by adenosine or adenosine deaminase, and in particular leukemia. Further Applicant claims methods to treat a patient using such compositions in various pharmaceutical formulations.

As set forth supra, BMS teaches that the acid lability of 2,'3'-didoxypurine nucleosides, and in particular, 2',3'-dideoxyadenosine (ddA), 2',3'-dideoxyinosine (ddI) and 2',3'-dideoxyguanosine (ddG) and their triphosphates are well-known in the art. See page 2, lines 9-25. Approaches to improve the acid stability of these acid-labile antiviral nucleoside derivatives have involved enteric-coated formulations, inclusion of a buffer in the dosage form, and neutralization of the gastrointestinal tract just before drug ingestion by pretreatment with

commercial antacids. Further, BMS teaches on page 3, lines 30-36, that the buffers applied as antacid agents include mixtures of water-insoluble antacid magnesium compounds with dihydroxyaluminum alkali metal carbonates or calcium carbonate, preferably with calcium carbonate. BMS discloses in Example 4, various oral tablet formulations with didanosine and calcium carbonate using microcrystalline cellulose and polyplasdone XL10 for use as antiviral agents.

BMS does not specifically teach that analogs, pentostatin or cladribine, can be administered with the antacid. Further, BMS does not explicitly state that the compositions can be used in the treatment of hematological malignancies, solid tumors sensitive to 2'-deoxyadenosine analogs or adenosine deaminase inhibitors and autoimmune diseases mediated by adenosine or adenosine deaminase, and in particular leukemia. Finally, BMS may not specifically disclose the particular pharmaceutical formulations.

CARSON teaches 2'-halo-2-deoxyadenosine compounds, and in particular 2'-chloro-2'-deoxyadenosine, also known as cladribine, for the treatment of monocyte-mediated disorders, such as rheumatoid arthritis and multiple sclerosis. See abstract and column 6, lines 37-65. Further, in column 4, line 56 to column 5, line 14, CARSON discloses that 2'-chloro-2'-deoxyadenosine has been found to be effective for the treatment of chronic lymphocytic leukemia and some T cell malignancies. CARSON teaches in column 14, lines 53-59, that oral administration of the compound is a particularly attractive mode of administration; however, the bioactive compounds potentially decompose in the acidic conditions of the stomach. CARSON teaches that this decomposition is due to the hydrolysis of the glycosidic bond under acidic conditions. In column 13, line 48 to column 14, line 41, CARSON discloses various

pharmaceutical formulations. In particular, in column 13, line 60 to column 14, line 3, CARSON discloses liposomal formulations using phosphatidyl cholines. In column 14, lines 27-41, CARSON discloses enteric formulations that serve to resist disintegration in the stomach and permits the active ingredient to pass intact into the duodenum. Examples of such enteric layers or coatings include cellulose acetate phthalate and the like.

GALLAGHER teaches pentostatin for the treatment of cerebral and cardiovascular disorders. See Abstract. Further, GALLAGHER teaches in column 2, lines 30-53 that pentostatin is a potent inhibitor of the enzyme adenosine deaminase. In column 7, line 12 to column 8, line 2, GALLAGHER discloses various pharmaceutical formulations. In particular, in column 7, lines 30-34, GALLAGHER teaches that pentostatin can be administered with magnesium carbonate, methylcellulose, sodium carboxymethylcellulose and the like.

It would have been obvious to one of ordinary skill in the art to make and use compositions comprising a 2'-deoxyadenosine analog, including pentostatin or cladribine, with an antacid to prevent decomposition in the stomach via hydrolysis of the glycosidic bond under acidic conditions. By Applicant own admission in the present specification, calcium carbonate is a conventional pharmaceutical additive. See page 24, line 21 to page 25, line 20, and in particular, page 25, line 19. As CARSON and GALLAGHER teach that cladribine and pentostatin are useful in the treatment of leukemia and diseases mediated by adenosine deaminase, respectively, a skilled artisan would have been motivated and have had a reasonable expectation of success to make and use acid-stabilized pharmaceutical compositions with cladribine or pentostatin for its known indication, in combination with an antacid such as calcium carbonate, as per BMS, optionally formulated with an enteric layer or coating, erodible

matrix or as a solid dispersion. Other particular pharmaceutical formulations, for example controlled release formulations, complexes with ion exchange resins and microspheres, are seen as a choice of experimental design, are well known to a skilled artisan and are within the purview of the prior art.

Claims 11, 16, 20, 44-48, 50-52 and 54-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over patent EP 0 524 579 A1 to BRISTOL-MYERS SQUIBB COMPANY (BMS) in view of THE MERCK INDEX, Twelve Edition, **1996**, 2337.

Applicant claims methods to treat a patient using acid labile 2'deoxyadenosine analogs and an agent that reduces that acidic environment of the stomach, and in particular an antacid such as calcium carbonate, a H2 inhibitor such as cimetidine, or proton pump inhibitor.

As set forth supra, BMS teaches that the acid lability of 2,'3'-didoxypurine nucleosides, and in particular, 2',3'-dideoxyadenosine (ddA), 2',3'-dideoxyinosine (ddI) and 2',3'-dideoxyguanosine (ddG) and their triphosphates are well-known in the art. See page 2, lines 9-25. Approaches to improve the acid stability of these acid-labile nucleoside derivatives have involved enteric-coated formulations, inclusion of a buffer in the dosage form, and neutralization of the gastrointestinal tract just before drug ingestion by pretreatment with commercial antacids. Further, BMS teaches on page 3, lines 30-36, that the buffers applied as antacid agents include mixtures of water-insoluble antacid magnesium compounds with dihydroxyaluminum alkali metal carbonates or calcium carbonate, preferably with calcium carbonate. BMS discloses in Example 4, various oral tablet formulations with didanosine and calcium carbonate using microcrystalline cellulose and polyplasdone XL10 for use as antiviral agents.

BMS does not specifically disclose the use of the commercial antacid, cimetidine, also known as Tagamet, in particular. Further, BMS does not explicitly state that the compound that can be used for neutralization of the gastrointestinal tract can be a proton pump inhibitor.

THE MERCK INDEX teaches that cimetidine is a histamine H2-receptor antagonist that inhibits gastric acid secretion.

It would have been obvious to one of ordinary skill in the art to use 2'-deoxyadenosine analogs with any compound known to neutralize of the gastrointestinal tract, as BMS teaches that such techniques are conventional in attempts to increase the bioavailability of acid-labile nucleosides. A skilled artisan would have been motivated and have had a reasonable expectation of success to make and use compositions with acid-labile 2'-deoxyadenosine analogs in combination or alternation with an agent known to neutralize the gastrointestinal tract, such as a histamine H2-receptor antagonist that inhibits gastric acid secretion, or a proton pump inhibitor. The choice of which particular agent, of the numerous agents known in the art, to neutralize the gastrointestinal tract, is seen as a choice of experimental design, are well known to the skilled artisan, and are considered well within the purview of the prior art.

Claims 11, 13-20, 24, 26-27, 29, 46-47, 49-50, 52 and 56-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over patents US 5,118,672 ('672) and US 5,159,067 ('067) both to SCHINAZI et al. in view of patent US 5,194,464 to ITOH et al.

Applicant claims methods to treat a patient using acid labile 2'deoxyadenosine analogs and an agent that reduces that acidic environment of the stomach. Further, Applicant claims methods to treat a patient using said compositions formulated with an enteric coating or layer,

erodible matrix, solid dispersion, complex with an ion exchange resin, microspheres or a controlled release mechanism.

As set forth supra, SCHINAZI teaches in column 30, line 66 to column 31, line 8 of the '672 patent and column 13, lines 52-63 of the '067 patent, that some compounds useful in methods to treat viral infection, such as 2',3'-dideoxyadenosine and 2',3'-dideoxy-N^6-methyladenosine, and their diphosphohexose derivatives are acid labile. Further, in the same passages, SCHINAZI teaches that if oral administration of these antiviral nucleoside analogs is desired, the compound must be provided in a composition that protects it from the acidic environment of the stomach, in combination with an antacid formulation and/or in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. In column 31, lines 19-39 and column 31, line 62 to column 32, line 9 of the '672 patent and column 14, lines 4-24 and column 14, line 47 to column 15, line 9 of the '067 patent, SCHINAZI discloses various pharmaceutical formulations, including various binders, coatings and controlled release formulations.

SCHINAZI may not specifically disclose the particular pharmaceutical formulations recited in the present claims.

ITOH discloses enteric films that excel in film strength and acid resistance for use in pharmaceutical preparations. See abstract. "Generally, enteric coating of pharmaceutical preparations has been carried out for the purposes of the protection of the active ingredient susceptible of the protection of the gastric juice and the drug-release controlled system (or the drug delivery system)" column 1, lines 9-13. In column 1, lines 62-68, ITOH teaches that the enteric coating includes hydroxypropylmethylcellulose phthalate (HPMCP). ITOH further

discloses in column 2, line 68 that the formulations can include as the active ingredient, adenosine phosphate. Further, ITOH discloses in column 3, line 11 that the formulations can include as an additive, calcium carbonate.

It would have been obvious to one of ordinary skill in the art to use the pharmaceutical compositions of SCHINAZI in combination with the enteric formulations of ITOH, as SCHINAZI teaches that if oral administration is desired, compositions can be provided in combination with an antacid formulation and/or in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine, such as the enteric coating of ITOH. A skilled artisan would have been motivated and have had a reasonable expectation of success to make and use compositions comprising the nucleoside analogs of SCHINAZI with an antacid, such as calcium carbonate, formulated with an enteric coating or layering, such as one taught by ITOH. Other particular pharmaceutical formulations, for example controlled release formulations, complexes with ion exchange resins and microspheres, are also well known in the art, are seen as a choice of experimental design, are well known to a skilled artisan and are within the purview of the prior art.

Claims 11, 13-20, 24, 26-27, 29, 46-47, 49-50, 52 and 56-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over patents US 5,118,672 ('672) and US 5,159,067 ('067) both to SCHINAZI et al. in view of patent US 5,824,339 to SHIMUZU et al.

Applicant claims methods to treat a patient using acid labile 2'deoxyadenosine analogs and an agent that reduces that acidic environment of the stomach. Further, Applicant claims methods to treat a patient using said compositions formulated with an enteric coating or layer,

erodible matrix, solid dispersion, complex with an ion exchange resin, microspheres or a controlled release mechanism, such as effervescent drug absorption system (EFVAS).

As set forth supra, SCHINAZI teaches in column 30, line 66 to column 31, line 8 of the '672 patent and column 13, lines 52-63 of the '067 patent, that some compounds useful in methods to treat viral infection, such as 2',3'-dideoxyadenosine and 2',3'-dideoxy-N^6-methyladenosine, and their diphosphohexose derivatives are acid labile. Further, in the same passages, SCHINAZI teaches that if oral administration of these antiviral nucleoside analogs is desired, the compound must be provided in a composition that protects it from the acidic environment of the stomach, in combination with an antacid formulation and/or in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. In column 31, lines 19-39 and column 31, line 62 to column 32, line 9 of the '672 patent and column 14, lines 4-24 and column 14, line 47 to column 15, line 9 of the '067 patent, SCHINAZI discloses various pharmaceutical formulations, including various binders, coatings and controlled release formulations.

SCHINAZI may not specifically disclose the particular pharmaceutical formulations recited in the present claims.

SHIMIZU teaches effervescent compositions comprising a physiologically active substance, an enteric coating, en effervescing component and an auxiliary effervescing agent that provides for the controlled release of the physiologically active substance. See abstract. SHIMIZU further discloses in column 5, lines 32-33 that the physiologically active substance can be adenosine triphosphate. Further, SHIMIZU discloses in column 6, line 40 that the formulations can include as an additive, calcium carbonate.

It would have been obvious to one of ordinary skill in the art to use the pharmaceutical compositions of SCHINAZI in combination with the effervescent drug absorption system (EFVAS) of SHIMIZU, as SCHINAZI teaches that if oral administration is desired, compositions can be provided in a composition that protects it from the acidic environment of the stomach, such as with the effervescent drug absorption system (EFVAS) of SHIMIZU. A skilled artisan would have been motivated and have had a reasonable expectation of success to make and use compositions comprising the nucleoside analogs of SCHINAZI with an additive, such as calcium carbonate, formulated with an effervescing agent, such as one taught by SHIMIZU, for controlled release of the acid-sensitive nucleoside analog. Other particular pharmaceutical formulations, for example other particular controlled release formulations, complexes with ion exchange resins and microspheres, are also well known in the art, are seen as a choice of experimental design, are well known to a skilled artisan and are within the purview of the prior art.

Claims 11, 13-20, 24, 26-27, 29, 46, 49-50, 52 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over patents US 5,118,672 ('672) and US 5,159,067 ('067) both to SCHINAZI et al. in view of patent US 5,518,730 to FUISZ.

Applicant claims methods to treat a patient using acid labile 2'deoxyadenosine analogs and an agent that reduces that acidic environment of the stomach. Further, Applicant claims methods to treat a patient using said compositions formulated with an enteric coating or layer, erodible matrix, solid dispersion, complex with an ion exchange resin, microspheres or a controlled release mechanism.

As set forth supra, SCHINAZI teaches in column 30, line 66 to column 31, line 8 of the '672 patent and column 13, lines 52-63 of the '067 patent, that some compounds useful in methods to treat viral infection, such as 2',3'-dideoxyadenosine and 2',3'-dideoxy-N^6-methyladenosine, and their diphosphohexose derivatives are acid labile. Further, in the same passages, SCHINAZI teaches that if oral administration of these antiviral nucleoside analogs is desired, the compound must be provided in a composition that protects it from the acidic environment of the stomach, in combination with an antacid formulation and/or in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. In column 31, lines 19-39 and column 31, line 62 to column 32, line 9 of the '672 patent and column 14, lines 4-24 and column 14, line 47 to column 15, line 9 of the '067 patent, SCHINAZI discloses various pharmaceutical formulations, including various binders, coatings and controlled release formulations.

SCHINAZI may not specifically disclose the particular pharmaceutical formulations recited in the present claims.

FUISZ teaches controlled release delivery systems using melt spun biodegradable polymers as carriers for bio-effecting agents. See abstract. FUISZ discloses in column 9, lines 62-65, that in oral formulations, the polymer "must provide a similar protective and delivery function." Further, FUISZ further discloses in column 8, line 56 that the bio-effecting agent can be pentostatin. FUISZ discloses in column 9, line 62 to column 10, line 65 various additives that can also be added for oral formulation.

It would have been obvious to one of ordinary skill in the art to use the pharmaceutical compositions of SCHINAZI in combination with the controlled release system of FUISZ, as

SCHINAZI teaches that if oral administration is desired, compositions can be provided in a composition that protects it from the acidic environment of the stomach, such as with the protective controlled release system of FUISZ. A skilled artisan would have been motivated and have had a reasonable expectation of success to make and use compositions comprising the nucleoside analogs of SCHINAZI with an additive, such as calcium carbonate, formulated with protective polymer, such as one taught by FUISZ, for controlled release of the acid-sensitive nucleoside analog. Other particular pharmaceutical formulations, for example other particular controlled release formulations, complexes with ion exchange resins and microspheres, are also well known in the art, are seen as a choice of experimental design, are well known to a skilled artisan and are within the purview of the prior art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

Claims 1-24, 26-27, 29 and 38-58 are pending. Claims 1-10 and 38-43 are withdrawn. Claims 11-24, 26-27, 29 and 44-58 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Josephine Young whose telephone number is (703) 605-1201. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (703) 308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

JY
April 4, 2003

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600